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(71) Applicants  
Imperial Chemical  
Industries PLC,  
(United Kingdom),  
Imperial Chemical House,  
Millbank,  
London SW1P 3JF  
(72) Inventors  
Dr William George  
Rathmell  
Dr Anthony Michael  
Skidmore  
Dr Margaret Claire  
Shephard  
Dr Brian Conrad Baldwin  
(74) Agent and/or  
Address for Service  
Henry Givven Hamilton  
Alner,  
Imperial Chemical  
Industries PLC,  
Legal Dept,  
Patents,  
Thames House North,  
Millbank,  
London SW1P 4QG

**(54) Fungicidal compositions**

(57) Fungicidal compositions displaying "resistance breaking" effects and/or synergy, and having broader spectra of activity, comprise a fungicide (or co-fungitoxicant) which inhibits adenosine deaminase or blocks sterol biosynthesis in fungi and a further fungicide having a different mode of action.

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## SPECIFICATION

## Fungicidal compositions

- 5 This invention relates to compositions for combat-  
ing plant fungi. More particularly the invention  
relates to mixtures of fungicidal substances contain-  
ing a first fungicide which is either an inhibitor of  
adenosine deaminase or of sterol biosynthesis in  
10 fungi and at least one other anti-fungal substance  
having a different mode of anti-fungal effect.

- It is known that plant fungi, especially races  
(strains, types) thereof, can develop resistance to,  
that is become insensitive to, anti-fungal chemicals  
15 thereby reducing the efficacy of a particular chemical.  
Indeed there are believed to be in existence  
certain plant fungal pathogens which are resistant to  
fungicides of the type which combat them, for  
example, by inhibiting their ability to biosynthesise  
20 certain steroids essential to their metabolism, for  
example ergosterol. These fungicides, more specifically  
either block the incorporation of acetate into  
ergosterol an essential metabolic pathway of the  
fungus, thereby disrupting the synthesis and function  
25 of cell membranes by the fungus. Plant  
pathogens of the latter type include, in particular,  
races etc., of powdery mildew diseases such as  
*Erysiphe graminis* which infect cereal plants, for  
example crops of barley and wheat, and mildews  
30 which infect non-cereal crops such as vines and  
apples, such latter diseases being, for example,  
*Uncinula necator*, *Podosphaera leucotricha* and  
*Sphaerotheca fuliginea* or other diseases such as  
*Venturia inaequalis* on apples or *Cercospora* leaf  
35 spots on peanuts, banana and sugar beet.

- It has now been found that certain mixtures of, or  
combinations of, fungicides are not only less prone  
than the individual components thereof to suffer  
from reduction in their efficacy due to resistant  
40 (insensitive) species of plant pathogens infecting  
crops upon which they are sprayed (or the seed  
pre-treated with them), but in addition often display  
synergism, that is to say the combined antifungal  
effect of the mixture is greater than that which would  
45 have been expected if the fungicidal components  
were acting separately. Such mixtures are ones in  
which a pyrimidine fungicide or a sterol biosynthesis  
inhibiting fungicide is combined with one or more  
fungicides having a different mode of action against  
50 the fungal pathogens being combated.

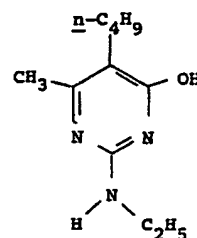
According to the present invention there is provided an anti-fungal composition comprising either, as a first ingredient, a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide

- 55 having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.

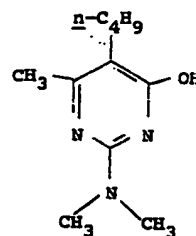
- The fungicide which inhibits adenosine deaminase  
60 in fungi may be a pyrimidine fungicide and by "a pyrimidine fungicide" is intended single ring compounds such as ethirimol, dimethirimol and bupirimate. The term is not intended to embrace bicyclic and tricyclic compounds in which a central carbon atom bears a pyrimidine ring and one or more other  
65 aryl or heterocyclic rings.

- The co-fungitoxicant need have no fungicidal activity in its own right; or have activity only against triazole resistant strains of a pathogen.

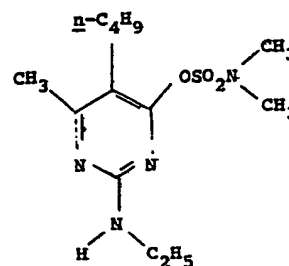
- 70 The fungicidal ethirimol is the subject of British Patent No. 1182584 and it has the chemical structure:-



- The fungicide dimethirimol is also the subject of  
British Patent No. 1182584 and it has the chemical  
75 structure:-



- The fungicide bupirimate is the subject of British  
Patent No. 1400710 and it has the chemical structure:-



- The foregoing fungicides are, as already stated,  
80 considered to have an anti-fungal effect by inhibition of the action of adenosine deaminase in the meta-

Certain of the /The Chemical/mathematical formula(e) appearing in the printed specification was/were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.

The matter shown in the printed specification between square brackets was furnished after the filing date of the application, the application as filed being defective as regards this matter.

This print embodies corrections made under Section 117(1) of the Patents Act 1977.

This print takes account of replacement documents later filed to enable the application to comply with the formal requirements of the Patents Rules 1982.

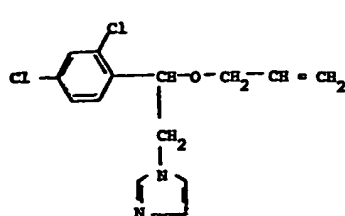
bolism of fungi.

In a further aspect, therefore, the invention provides an anti-fungal composition comprising a fungicide which is ethirimol, dimethirimol or bupirimate or an anti-fungal substance which is an inhibitor of the ability of the fungus to biosynthesise sterols and

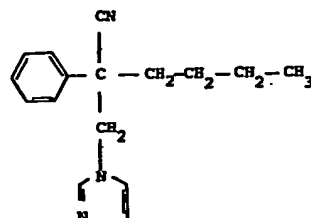
at least one further fungicide which has a different mode of action in combating fungi. Examples of fungicidal substances having the capacity to inhibit sterol biosynthesis and the classes to which the belong, are as follows:—

Table A	
CLASS AND COMMON NAME OF FUNGICIDE	TRADE NAMES OF FUNGICIDAL PRODUCTS CONTAINING THE FUNGICIDE
<i>Imidazoles</i>	
Imazalil	Fungaflor, present in Mist-O-Matic Murbenine Plus, Mist-O-Matic Muridal Seed Treatment
Prochloraz	Sportak
Fenaponil	—
<i>Piperazines</i>	
Triforine	Saprol, Triforine LST, present in Nimrod T
<i>Pyridines</i>	
Buthlobate	Parnon
EL 241	—
<i>Piperidines</i>	
Fenpropidin	—
<i>Pyrimidines</i>	
Fenarimol	Rubigan
Nuarimol	Triminol, present in Mist-O-Matic Murox Seed Treatment
Triarimol	—
<i>Triazoles</i>	
Bitertanol	—
Diclobutrazol	Vigil, present in Vigil K, present in Vigil T
Fluotrimazole	Persulon
Propiconazole	Tilt 250 EC, in Tilt mbc 45WP
Triadimefon	Bayleton, Bayleton 5, in Bayleton, BM, Bayleton CF
Triadimenol	Baytan
Etaconazole	Vanguard, Sonax
PP969	—
<i>Morpholines</i>	
Dodemorph	BASF F238
Fenpropimorph	Corbel, Mistral
Tridemorph	Calixin, Bardew, Beacon, Cosmic

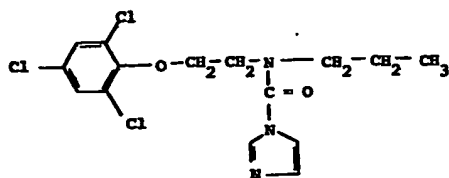
The chemical structures of the foregoing chemical substances are set out below:—

IMIDAZOLES

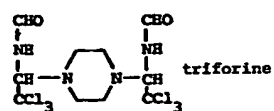
imazalil



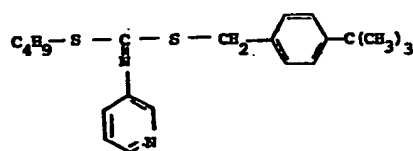
fenaponil

PIPERAZINES

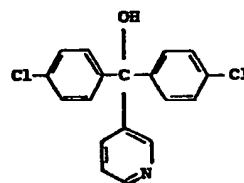
prochloraz



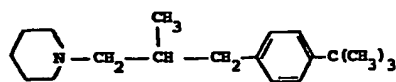
triforine

PYRIDINES

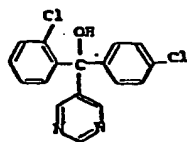
buthiobate



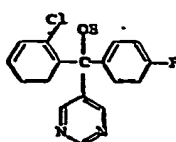
EL-241

PIPERIDINES

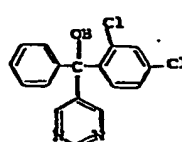
fenpropidin

PYRIMIDINES

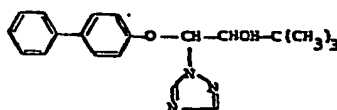
fenarimol



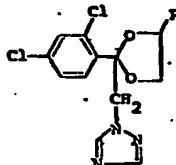
nuarimol



triarimol

TRIAZOLES

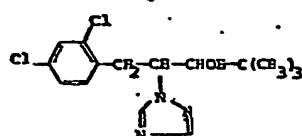
bitertanol



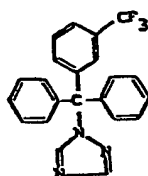
propiconazole CGA 64250

R=n-C<sub>3</sub>H<sub>7</sub>

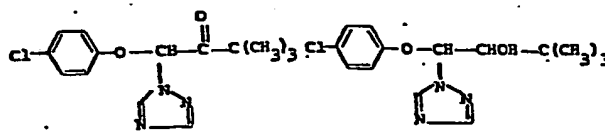
eteconazole CGA 64251

R=C<sub>2</sub>H<sub>5</sub>

diclobutrazol

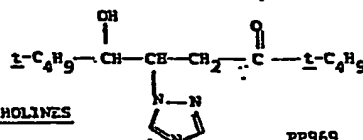
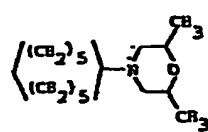


fluotrimazole

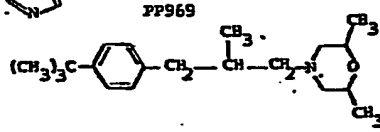


triadimefon

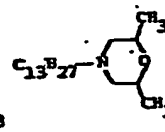
triadimenol

MORPHOLINES

dodemorph



fenpropimorph



tridemorph

In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance from the foregoing list of chemical compounds, and at least one further fungicidal substance having a mode of action in combating fungi which is different from that of the first fungicide.

As far as suitable further fungicidal substances are concerned these may be any general, i.e. metabolic, inhibitor of plant fungal growth, for example a respiratory inhibitor.

By the term "general metabolic inhibiting agent" (including respiratory inhibitors) are intended fungicidal and anti-fungal substances such as those listed below under chemical class headings with examples of specific fungicides listed and an indication of their believed mode of action.

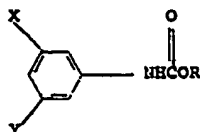
Table B

## 1: Site specific inhibitors

<i>Acyalalanies</i>	-furalaxyl, metalaxyl, ofurace, galben.
Mode of action	-?
<i>Antibiotics</i>	-cycloheximide etc.
Mode of action	-inhibits protein synthesis
<i>Benzimidazoles</i>	-benomyl, carbendazim, thiophanate methyl, thiabendazole, fuberidazole
Mode of action	-inhibition of mitosis
<i>Carboxamides</i>	-carboxin, oxycarboxin, methfuroxam, fenfuram, furmecyclox, benodanil, pyracarbolid
Mode of action	-interference with respiration by blocking succinate dehydrogenase
<i>Dicarboxamides</i>	-iprodione, procymidon, vinclozolin, M8164 (Serinal)
Mode of action	-interference with mitotic segregation
<i>Aromatic hydrocarbons</i>	-2-phenylphenol, sodium -o-phenylphenate biphenyl, chloroneb, dichloran, quintozone, tecnazene.
Mode of action	-interference with mitotic segregation
<i>Dinitrophenols</i>	-dinapacryl, dinocap
Mode of action	-uncouplers of oxidative phosphorylation
<i>Dimethyldithiocarbamates</i>	-thiram
Mode of action	-inhibitors of pyruvate dehydrogenation
<i>Guanidines</i>	-dodine, guazatine
Mode of action	-affect cell membrane permeability
<i>Organotin compounds</i>	-fentin
Mode of action	-inhibition of oxidative phosphorylation
<i>Organic phosphates and isoprothiolane</i>	-pyrazophos, edinfenphos, BP, isoprothiolane
Mode of action	-inhibition of the conversion of phosphatidyl-ethanolamine to phosphatidyl-choline
<i>Acetamides</i>	-curzate
Mode of action	-unknown
<i>Aminobutane</i>	-2-aminobutane
Mode of action	-inhibition of pyruvic dehydrogenase
<i>Anthraquinones</i>	-dithianon
Mode of action	-inhibition of glycolysis
<i>Isoxazolones</i>	-drazoxalon
Mode of action	-uncoupler of respiration
<i>Nitroisophthalates</i>	-nitrothal-isopropyl
Mode of action	-unknown
<i>Organic phosphates</i>	-ditalimfos
Mode of action	-disrupts metabolism
<i>Quinoxalines</i>	-quinomethionate
Mode of action	-?
<i>Sulphamides</i>	-dichlofluanid, tolyfluanid
Mode of action	-?
<i>Thiocarbamates</i>	-prothiocarb, propanocarb
Mode of action	-causes cell membrane disfunction

*N*-Phenylcarbamate derivatives

Such as those disclosed in European Patent Application No. 81109561.1 (Publication No. 51871) having the general formula:



5 where X and Y are alkyl, alkoxy or halogen and R is methol or ethyl.

Table C

<i>Thiadiazoles</i>	-etridazole
Mode of action	-interferes with respiration
<b>2. Multisite inhibitors</b>	
<i>Dithiocarbamates</i>	-maneb, zineb, mancozeb, nabam, propineb etc.
Mode of action	-inhibitors of thiol groups
<i>Phthalimides</i>	-captafol, captan, folpet
Mode of action	-inhibitors of thiol groups
<i>Phthalonitriles</i>	-chlorothalonil
Mode of action	-inhibitor of thiol groups
<i>Copper compounds</i>	-various
Mode of action	-?
<i>Mercury compounds</i>	-various
Mode of action	-?
<i>Sulphur</i>	-
Mode of action	-?
<i>Aluminium compounds</i>	-FOSETYL ALUMINIUM
Mode of action	-?

*Anionic agents*

Sodium dodecylbenzene sulphonate  
 Sodium dodecylsulphate  
 Sodium C13/C15 alcohol ether sulphonate  
 Sodium ceto stearyl phosphate ester  
 Dioctyl sodium sulphosuccinate  
 Sodium isopropyl naphthalene sulphonate  
 Sodium methylene bis naphthalene sulphonate

*Cationic agents*

Cetyl trimethyl ammonium chloride  
 Salts of long chain primary, secondary or tertiary amine  
 Alkyl propylene amines  
 Lauryl pyridinium bromide  
 Quaternised fatty amine ethoxylate  
 Alkyldimethyl benzyl ammonium chloride  
 1 - Hydroxyethyl - 2 - alkyl imidazoline.

In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance from the foregoing list of chemical compounds, and at least one further fungicidal substance having a mode of action in combating fungi which is different from that of the first fungicide and which is a substance chosen from the specific fungicidal subst-

ances recited in the immediately preceding list.

The invention also provides a process for treating seed which comprises dressing seed with a composition according to the invention.

In another aspect seed may be dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi and then with a further fungicide as defined above. Batches of seed treated separately with a first fungicide and with a further fungicidal substance may be mixed with untreated seed, e.g. tumbled therewith, so as to produce a

batch of treated seed.

The invention further provides, in yet another aspect, a process for combating plant fungi which comprises applying to a plant, to seed of a plant, or to the locus of a plant or seed, an anti-fungal composition as defined in any of the preceding paragraphs.

In a still further aspect the invention provides a process of combating plant fungi which comprises alternately treating, e.g. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicidal substance as defined above.

The amounts of fungicidal substance used in the invention compositions can readily be determined by simple experimentation, but in general, in view of the ability to counter resistant (insensitive) races etc., of fungi and/or the synergism displayed, it is not necessary to use the full rates of chemical normally applied.

#### EXAMPLE 1

A series of initial experiments were carried out to determine the efficacy of a range of co-fungitox-icants in controlling two isolates of *E. graminis* f.sp *hordei* in the absence of triadimefon with the following results (Table 1).

Sumisclex showed activity against one or both fungus isolates whereas Sanspor and Terrazole were inactive.

Sumisclex was further tested to determine in more detail its rate response against the two isolates of *E. graminis* f.sp *hordei* (Table 2). Based on these data, suboptimal rates of this compound were chosen for a further interaction experiment involving triadimefon (Tables 3 and 4).

Against both isolates the addition of Sumisclex at 150 ppm to triadimefon at 0.1 ppm boosted the activity of triadimefon in the degree of disease control achieved. The margin of this increase in activity must be accounted for by a synergistic interaction between the two compounds.

#### Materials and Methods.

1. **Plant Sowing:** Approximately 10 seeds/pot of Golden Promise spring barley were sown into John Innes compost number one in minipots.

1.1 **Growth Conditions:** Day temperature 21°C, Relative Humidity 60%, Night temperature 17°C, Relative Humidity 95%, 16 hours daylength. The plants were watered by an automatic watering system.

2. **Test Method for spraying the plants:** Plants were sprayed at 6 days old; the chemicals under test were made up in 0.03% Tween 20; and the plants were sprayed to give an even coverage on both leaf surfaces, using a hand-held De Vilbiss spray gun at 15 psi (pounds per square inch).

After spraying, the plants were transferred to a second growth chamber for 24 hours to allow plants to dry.

2.1 **Growth Conditions in this room were:** Day temperature 24°C, Relative Humidity 60%, Night temperature 17°C, Relative Humidity 95%, 16 hours daylength. The plants were watered by an automatic watering system.

3. **Method for preparing the repli dishes:** Plants

were removed from the Growth Room and cut into 2 cm lengths from just below the tip of the prophyll. Only uniform plants were chosen. Only one leaf piece was taken from each prophyll. The cut leaf pieces were then placed into a slit in the agar in the repli dish. (the dishes contained 45 ml of 10% Tap water agar), the top rate of chemical first proceeded by lower rate. For each chemical rate there were 5 replicate leaf pieces.

When changing from one rate of chemical to a lower rate the scissors and forceps were wiped with a swab soaked in Methanol to avoid contamination. Particular attention was paid to ensure that the leaf pieces did not touch the lid nor overlap one another in the dish. The former would cause condensation to run down the leaf pieces and could wash off some spores, the latter would lead to uneven inoculation and hence misleading results.

4. **Inoculation Method:** Infected leaf pieces were cut from stock plants in propagating tubes and placed in petri dishes on moist foam squares 48 hours prior to inoculation. The infected leaf pieces were kept in a 19°C constant temperature room with a 16 hour day length.

Repli dishes were inoculated using a settling tower, the tower was placed over the opened repli dish and sporulating leaf pieces held in forceps were placed in the nose of the tower. An air line set at 3/4 lb per square inch pressure was used to blow the spores off the leaf pieces and into the settling tower.

The repli dishes remained inside the tower for 2 minutes after which the tower was removed and the lid replaced on the repli dish. The tower, forceps and air lines were swabbed with Methanol to decontaminate them.

Once all the repli dishes were inoculated they were placed in a 19°C constant temperature room with a 16 hour daylength where they remained until assessment 6 days later.

5. **Assessment:** Percentage sporulating disease was assessed on each leaf piece.



**TABLE 1**  
**Disease Control**  
*Erysiphe graminis f.sp hordei*  
isolate

Fungitoxicant	Rate ppm ai.	1	2
Sumisclex (procymidone)	500	99	100
	250	98	100
	125	65	39
	100	93	56
	50	98	25
	0	0	0

**TABLE 2**  
**2 % Disease Control**  
*Erysiphe graminis f.sp hordei*  
isolate

Fungitoxicant	Rate ppm ai.	1	2
Sumisclex (procymidone)	250	99	87
	200	96	30
	175	97	69
	150	27	57
	125	22	27
	0	0	0

**TABLE 3**  
**Isolate 1 % Disease Control**

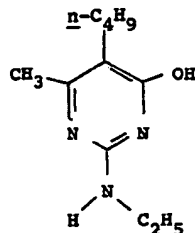
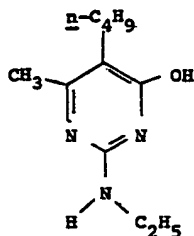
	Triadimefon Rate ppm ai	Triadimefon + 150 ppm Sumisclex
	0.25	—
	0.1	59 (20)
	0.05	30
	0.025	43
	0.01	—
Sumisclex	150	0
Untreated	—	0
Actual	74%	
untreated		
disease		
level		
( ) = Activity of triadimefon alone in same test dish at 0.1 ppm.		

**TABLE 4**  
**Isolate 2 % Disease Control**

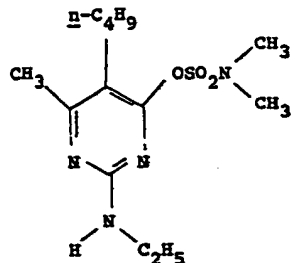
	Triadimefon Rate ppm ai	Triadimefon + 150 ppm Sumisclex
	0.5	93 (52)
	0.25	0
	0.1	—15
	0.05	
Sumisclex	150	—31
Untreated	—	0
Actual		
Untreated		61%
Disease level		
( ) = Activity of triadimefon in same test dish at 0.1 ppm.		

# CLAIMS

1. An anti-fungal composition comprising as a first ingredient either a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.
2. An anti-fungal composition according to claim 1 comprising an adenosine deaminase inhibitor which is a pyrimidine derivative having the structure:



or



3. An anti-fungal composition according to claim 1 comprising a fungicide having a sterol biosynthesis blocking mode of action and which is an imidazole, piperazine, pyridine, piperidine, pyrimidine, triazole or morpholine derivative as hereinbefore defined.
4. An anti-fungal composition according to any of the preceding claims wherein the further fungicide is a site specific inhibitor or multisite inhibitor, as hereinbefore defined, or a general, eg. metabolic, inhibitor of fungal growth.
5. An anti-fungal composition according to any of the preceding claims wherein the further fungicide comprises any of the specific fungicidal substances defined hereinbefore.
6. A process for treating seed which comprises dressing seed with a composition according to the invention.
7. A process for dressing seed wherein seed is dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicide as defined in any of the

35 preceding claims.

8. A process for combating plant fungi which comprises applying to a plant, to seed of a plant, or to the locus of a plant or seed, an anti-fungal composition as defined in any of the preceding claims.

9. A process of combating plant fungi which comprises alternately treating, eg. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicidal substance as defined above.

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